

**REMARKS**

Responsive to the Notice of Non-Compliant Amendment (37C.F.R. §1.121) mailed January 6, 2005, Applicants submit a revised Response to the Office Action mailed June 18, 2004. The revised Response has been changed to reflect a complete listing of all the claims. Entry of the amendments and remarks contained in the Response filed herewith is respectfully requested.

Claims 49-65 are pending. Claims 49, 51, 53 and 59 have been amended above and claim 55 has been cancelled. Following entry of the amendments, claims 49-54 and 56-65 will be under examination. Support for the amendments can be found throughout the application as of its priority date. Specifically, support for the amendment to claim 49, can be found at, for example, in Figure 1, state 14, and at page 8, first paragraph, line 2. Support for the amendments to claims 51 and 59, can be found at, for example, page 8, first full paragraph. Support for the amendment to claim 53 can be found in cancelled claim 55. Accordingly, the amendments do not raise an issue of new matter and entry thereof is respectfully requested. Applicant has reviewed the rejections set forth in the Office Action mailed June 18, 2004, and respectfully traverses all grounds for the reasons that follow.

Applicant thanks the Examiner for her time and consideration during the personal interview conducted on November 24, 2004, with Dr. Bernhard Palsson and the undersigned licensee's representative. The above amendments and remarks below are believed by Applicant to be consistent with the points discussed during the interview.

**Rejections Under 35 U.S.C. § 112**

Claims 49-65 stand rejected under 35 U.S.C. § 112, first paragraph, for lacking written description allegedly because the claims contain subject matter which was not described in the specification to convey to one skilled in the art that the inventor had possession of claimed invention. In this regard, the Office asserts that the support found at pages 6-8 of the specification describes a procedure for creating metabolic genotypes from genomic data and a procedure for producing an *in silico* strain from the metabolic genotype where second procedure includes creating a genome specific stoichiometric matrix. The Office sets forth various

rejections alleging lack of written description based on the cited support. Applicant will respond to each rejection in turn.

Claim 49 stands rejected for lack of written description in the application as filed allegedly because the claimed method fails to recite "obtaining" a DNA sequence of a genome. The Office refers to Figure 1, state 14, as support for the assertion the application fails to contemplate a method where this step is not performed. Claim 49 additionally is alleged to lack written description for determining genes which "relate" to cellular metabolism although the concept of determining genes "involved" in cellular metabolism is acknowledged to be described.

The test for adequacy of written description is whether a person of ordinary skill in the art would recognize that the applicant possessed what is claimed. *Noelle v. Lederman*, 355 F.3d 1343, 1348 (Fed. Cir. 2004) (citing *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991)). Moreover, "[t]o comply with written description, it is not necessary that the application describe the claimed invention in *ipsis verbis*." *Application of Edwards*, 568 F.2d 1349, 1351-52 (C.C.P.A. 1978).

Applicant submits that the specification provides sufficient support to satisfy the written description requirement for the invention as claimed. For example, and as pointed out during the interview, the application describes obtaining genes, determining an opening reading frame of a gene or obtaining and determining an opening reading frame of a gene. The application additionally describes the concept of genes that relate to a protein's function, including cellular metabolism. In light of these descriptions of various combination of steps and of a gene and its related protein's function, Applicant respectfully submits that the application as filed as of its priority date provides sufficient written description of the claimed invention to satisfy the requirements of 35 U.S.C. § 112, first paragraph. Nevertheless, to further prosecution of the claimed subject matter, Applicant has amended claim 49 above to recite the step of obtaining a DNA sequence of a genome. Claim 49 also has been amended to recite the term "involved" rather than "relates" as suggested by the Examiner. Accordingly, these grounds of rejection are moot and withdrawal is respectfully requested.

Claims 51 and 59 stand rejected for lack of written description in the application as filed allegedly because the claimed categories correspond to a subset of those categories recited on page 8 of the application. Applicant respectfully points out that the application does not teach that the categories exemplified at page 8, first full paragraph, are the sole categories of genes that can be used for producing the claimed stoichiometric matrix. Nevertheless, to further prosecution of this application, claims 51 and 59 have been amended above to recite those categories listed on page 8, first full paragraph. Accordingly, this ground of rejection is moot and withdrawal is respectfully requested.

Claims 53 and 61 stand rejected for lack of written description in the application as filed allegedly because it does not require determination of a biomass composition as shown, for example, in Figure 2. Applicant again points out that the Figures are exemplary of one embodiment of the claimed methods. For example, the application describes that the claimed calculation of metabolic demand can be determined from the dry weight composition of the organism. Nevertheless, to further prosecution of this application, claims 53 and 61 have been amended to recite determination of the biomass composition. Accordingly, this ground of rejection is moot and withdrawal is respectfully requested.

Claim 53 also stands further rejected for lack of written description allegedly because it does not require performing flux balance analysis to produce an *in silico* strain of the microbial organism. Applicant respectfully draws the Examiner's attention to the preamble of claim 53, which is directed to producing an *in silico* representation. The *in silico* representation is complete following combining metabolic demands and uptake rates with a stoichiometric matrix as claimed in claim 53. Solving linear equations such as that exemplified in state 64 of Figure 2 yields the capabilities of the metabolic system. For example, the application describes:

To determine the metabolic capabilities of a defined metabolic genotype Equation 1 is solved for the metabolic fluxes and the internal metabolic reactions. . . . The solutions to Equation 1 lie in a restricted region. This subspace defines the capabilities of the metabolic genotype of a given organism, since the allowable solutions that satisfy Equation 1 and any constraints placed on the fluxes of the system define all the metabolic flux distributions that can be achieved with a particular set of metabolic genes. The particular utilization of the metabolic genotype can be defined as the metabolic phenotype that is expressed under those particular conditions.

Application, paragraph bridging pages 10-11.

Thus, claim 53 is directed to the *in silico* representation and not to the metabolic phenotype. Accordingly, requiring recitation of the step of solving linear equations would erroneously characterize the claimed *in silico* representation as a metabolic phenotype. Accordingly, the assertion in the Office Action that the application only contemplates flux balance analysis for combining the stoichiometric matrix and the other claimed calculations is not relevant to the claimed invention of producing an *in silico* representation and because the application specifically describes producing the representation as well as generating a metabolic phenotype as described above, for example. Further, the application contemplates linear programming other than flux balance analysis because state 64 of Figure 2 expressly recites general linear programming methods can be used to generate the metabolic phenotype. Accordingly, Applicant submits that claim 53 is supported by adequate written description and respectfully requests withdrawal of this ground of rejection.

Claims 57-61 stand rejected for lacking written description allegedly because repeating steps a) to d) and providing only metabolic genes, as compared to selecting the subset of metabolic genes from open reading frames found in the genome, lacks a basis in the application as filed.

Applicant submits that claims 57-61 contain adequate support in the application as filed. For example, the application describes a process that obtains nucleotide sequence information, identifies an open reading frame and assigns a function to the metabolic gene. This process is described throughout the application as filed, at pages 6-8 and in the Examples. The repetition of steps recited in claim 57 merely delineate the process describe therein and exemplified in Figure 1, for example. Performance of the claimed method on a gene by gene basis until a function is assigned before moving to the next gene is clear from the descriptions in the application and especially in light of the teachings in the application that the method can be:

[T]he systems and methods described herein can be implemented on any conventional host computer system.

Application at page 6, second paragraph. Moreover, the application is clear that the construction of a stoichiometric matrix can require iterations of one or more steps in the claimed method. In

this regard, the application describes the claimed method as a “process” (see, for example, page 6, last paragraph), which means “a progressive forward movement from one point to another on the way to completion.” *Webster's Third New International Dictionary, Unabridged. Merriam-Webster*, 2002. <http://unabridged.merriam-webster.com> (14 Dec. 2004). The application additionally teaches directly obtaining genes by selection from a database when the application describes:

One method for obtaining the nucleotide sequences in a genome is through commercial gene databases. Many gene sequences are available on-line though a number of sites (see, for example [ww.tigr.org](http://www.tigr.org)) and can easily be downloaded from the Internet.

Application at page 6, last paragraph.

Further, the application describes the steps in the claimed method as a process involving “selecti[ng]” (page 8, first paragraph), a “search” (page 8, first paragraph) as well as a process involving “gathering” (page 8, second paragraph and Figure 2). Each of these verbs indicate acts involving choosing, examining with a particular objective or a process of accumulation. *Webster's Third New International Dictionary, Unabridged. Merriam-Webster*, 2002. <http://unabridged.merriam-webster.com> (14 Dec. 2004). Accordingly, all of these teachings include construction of the claimed stoichiometric matrix iteratively, determining the function of one gene at a time, or stepwise, determining the function of all genes in one step. Moreover, the application describes supplementing steps of claim 57 when it teaches that additional reactions may be recognized upon review and included in the metabolic reaction list compiled by the claimed method. In this regard, the application describes:

Potentially, there may still remain a few reactions in cellular metabolism which are known to occur from *in vitro* assays and experimental data. These would include well characterized reactions for which a gene or protein has yet to be identified, or was unidentified from the genome sequencing and functional assignment of state 14 and 18. . . . [A]dditional metabolic reactions can be added to the list of metabolic reactions determined from the metabolic genotype from state 54 at a state 56. This would include information regarding the substrates, products, reversibility/irreversibility, and stoichiometry of the reactions.

Application at pages 8-9, bridging paragraph.

Further, the application describes in Example 1, paragraph bridging pages 13-14, that an *in silico* strain of *E. coli* was constructed that was “largely generated from annotated sequence data and from biochemical information” using “genetic sequence and open reading frame identifications and assignments [that are] readily available from a number of on-line locations (ex: [www.tigr.org](http://www.tigr.org)).” In addition to the previous description exemplifying the method of claim 57, it also is clear from the above description that the invention includes obtaining many or all sequences of a genome, identifying their open reading frames and assigning function as well as obtaining a sequence of a genome, identifying its open reading frame, assigning function and iterating these steps until many or all metabolic genes in the genome are identified.

In light of the descriptions in the application and the remarks above, Applicant submits that the method of claims 57-61 are adequately described to satisfy the written description requirement of section 112, first paragraph. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Claim 49 stands rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement allegedly because the application lacks guidance as to how to proceed if an open reading frame has little homology to genes encoding proteins of known function. In this regard, the Office asserts that the application lacks guidance for including or excluding sequences where a function has not been identified based on homology and that claim 57 implies that all metabolic genes in the genome must be determined. Lack of guidance is further asserted regarding discrimination between a metabolic gene and a non-metabolic gene, requiring undue experimentation for determining which genes to include as genes involved in cellular metabolism. The Office further asserts that the application lacks guidance relating to the level of sequence homology or criteria used to assign function and that the use of well-known methods in the art to practice the claimed method requires one to “use judgment, make independent decisions, and thus exercise inventive skill” allegedly because the well know methods are not provided in the application. The Office additionally asserts that the specification fails to provide guidance on how assignment of function provides to a gene provides the corresponding metabolic reaction. In support, the Office asserts that the teachings directed to reviewing biochemical literature and available experimental data requires undue experimentation allegedly because the claims embrace all genes of the microbial genome.

Applicant submits that the application enables the full scope of the invention as claimed. At the time the application was filed, those skilled in the art had been assigning function to an encoded gene product based on sequence homology for at least 15 years. The Federal Circuit case law on enablement is clear. The specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997). Moreover, it is well settled that “omission of minor details does not cause a specification to fail to meet the enablement requirement,” *Adang v. Fischhoff*, 286 F.3d 1346, 1358 (Fed. Cir. 2002), and that routine experimentation does not constitute undue experimentation. *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1360 (Fed. Cir. 1998). Further, enablement “does not require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect.” *CFMT, Inc. v. Yieldup International Corp.*, 349 F.3d 1333, 1338 (Fed. Cir. 2003). The subject application satisfies each of these rules of law.

Initially, Applicant points out that the assertion that practice of the claimed methods requires undue experimentation rising to the level of exercising “inventive skill” allegedly because well known methods are not provided in the application is unsupported. According to the term’s plain meaning, well known methods cannot require inventive skill because they are well known. Further, omission of minor details such as well known methods such as assignment of function based homology with other known sequences having known function does not preclude enablement of an invention, especially in a predictable art such as functional categorization based on sequence homology searching. *Adang*, 286 F.3d at 1358. Therefore, under recent Federal Circuit case law, Applicant is not required to teach, and preferably omits, that which is well known. *Id.* (see also *Hybritech Inc. v. Monoclonal Antibodies*, 802 F.2d 1367 (Fed. Cir. 1986)). Accordingly, following the teachings of the specification together with that which is well known in the art does not constitute undue experimentation nor inventive skill as asserted by the Office.

Use of judgment and making independent decisions is not the standard for measuring undue experimentation. Rather, routine experimentation is allowable. *Johns Hopkins Univ.*, 152 F.3d at 1360. Therefore, in contrast to that appearing to be asserted by the Office, an invention is

enabled without a roadmap requiring 100% predictability where sufficient guidance is provided even when one skilled in the art is required to use judgment and make decisions to practice the invention as claimed. As described previously, and further below, given the teachings and guidance in the application, those skilled in the art will know what decisions are required to be made and what effect such decisions will have on the claimed stoichiometric matrix or *in silico* representation given a level of sequence homology to a known gene having a known function. Further, the declaration by Dr. Subramaniam, attached as Exhibit A, attests that any experimentation, if at all, needed to compile the claimed stoichiometric matrix is well within the skill of those skilled in the art given the teachings and guidance in the application as filed. Therefore, Applicant submits that judgment or decision making processes by the user does not constitute undue experimentation because it was not undue given the well characterized and mature art of functional assignment based on sequence homology at the time the priority application was filed.

Regarding the state of the art and predictability of the functional assignment based on sequence homology criteria, the application teaches numerous methods well known in the art that allow gene identification based on sequence homology. For example, the application teaches that “[c]omputer programs for determining open reading frames are available, for example, by the University of Wisconsin Genetics Computer Group and the National Center for Biotechnology Information (page 7, first paragraph) and that “well established algorithms (i.e. the Basic Local Alignment Search Tool (BLAST) and the FAST family of programs can be used to determine the extent of similarity between a given sequence and gene/protein sequences deposited in the world wide genetic databases” (page 7, second paragraph). Each of these recited methods are well known and accepted methods for determining sequence homology and provide, for example, a percent sequence identity to closely related gene or protein sequences. As set forth in the attached declaration by Dr. Subramaniam, Exhibit A, acceptance of the gene as being an ortholog or non-orthologous gene replacement is well within the skill of those skilled in the art of bioinformatics. Moreover, the declaration further attests that the art of functional assignment based on sequence homology was a mature and predictable art at the time the application was filed. Therefore, the guidance provided in the application is sufficient to allow those skilled in the art to practice the claimed invention because it teaches well known methods for determining sequence homology and comparison to other genes and because it teaches one



skilled in the art to select a metabolic gene based on such sequence comparison. Further, the guidance provided in the application is sufficient to allow those skilled in the art to practice the claimed invention because criteria for making a functional assignment based on sequence homology is well known in the art and because the art is mature and predictable. The guidance provided in the application also is sufficient to allow those skilled in the art to practice the claimed invention because it satisfies the Federal Circuit precedent. *Adang*, 286 F.3d at 1358; *Johns Hopkins Univ.*, 152 F.3d at 1360.

Applicant further respectfully draws the Office's attention that a perfected embodiment or one that works with absolute predictability is not required to satisfy the enablement requirement of the first paragraph of § 112 unless that level of perfection or predictability is claimed. *CFMT, Inc.*, 349 F.3d at 1338. Applicant has not claimed the stoichiometric matrix or *in silico* strain at the level appearing to be required by the Office. The Office asserts that the specification lacks guidance for determining open reading frames and assigning function because criteria and guidance is not specified for making such selections. As described previously and attested to in the attached declaration by Dr. Subramaniam, Exhibit A, such selections and determinations are well known in the art. Moreover, where a gene is not identified to a function, those skilled in the art can omit it from the claimed method. In this regard, the application describes only that:

If a coding region from a gene in the target organism is homologous to a gene within one of the sequence databases, the open reading frame is assigned a function similar to the homologically matched gene. Thus, the functions of nearly the entire gene complement or genotype of an organism can be determined so long as homologous genes have already been discovered.

Application at page 7, second paragraph.

Therefore, the application teaches the inclusion of metabolic genes into the claimed stoichiometric matrix or the claimed *in silico* representation where homologous genes have been discovered. If the exclusion of one or more genes based on lack of sequence homology to a known gene occurs, regardless of the criteria used by one skilled in the art, then the effect will be merely a decrease in performance of the claimed stoichiometric matrix or *in silico* representation. Such a decrease in performance does not render the invention to lack enablement because

Applicant does not claim, nor is Applicant required to claim, a perfected level of performance.  
*Id.*

Regarding the assertion that the specification fails to enable the generation of a stoichiometric matrix based on functional assignment of gene product or protein because no guidance is provided as to the protein's corresponding metabolic reaction, Applicant submits that the term's plain meaning provides functional assignments. Most, if not essentially all, metabolic reactions are well known in the art. Given a metabolic function or the name of a metabolic protein it is routine to assign the biochemical reaction, including substrates, products and stoichiometry, because such reactions are prevalent in ordinary university text books. In support, Applicant attaches as Exhibit B, a Table of Contents from Stryer et al., *Biochemistry*, 4th ed., (1995) for Part III, that is directed to metabolism as well as an exemplary chapter on glycolysis that sets forth numerous known metabolic reactions, the name of the protein involved and the function of the protein based on its biochemical reaction. Various other biochemical reference books also set forth such reactions based on the function of the gene product. Accordingly, the claimed invention does not lack enablement because the field of metabolism is well known in the art.

In light of the above remarks, Applicant submits that the application sufficiently enables those skilled in the art to practice the invention as claimed. Withdrawal of this ground of rejection is respectfully requested.

Claims 54 and 65 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite allegedly because they fail to further define the methods of claims 53 and 61, directed to producing an *in silico* representation. The Office alleges that claiming the further step of performing a flux balance analysis (FBA) conflicts with the specification where it describes that FBA is performed in order to fully define the metabolic system.

Applicant submits that the further step of performing FBA as is claimed in claims 54 and 65 is sufficiently clear to particularly point out the subject matter Applicant regards as the invention. Further, claims 54 and 65 do not conflict with, and are consistent with, the descriptions in the application. As described previously, claims 54 and 61 are directed to producing an *in silico* representation. Such an *in silico* representation is the claimed combination

of the metabolic demands, uptake rate and the stoichiometric matrix. The *in silico* representation can be used to further define the metabolic system as described in the application at, for example, page 10, first and second paragraphs, and at pages 12-13, bridging paragraph. As described therein, the metabolic capabilities of an *in silico* representation can be solved using FBA to simulate metabolic capabilities under any number of conditions. Accordingly, claims 53 and 61 are directed to producing the underlying *in silico* representation that can be subjected to differing conditions to produce an output simulating metabolic capabilities under the subjected conditions. In contrast, claims 54 and 65 are directed to the method of subjecting the *in silico* representation to the conditions and producing the output. Such an output defines the state of a metabolic system under the specified conditions. Because claims 54 and 57 are directed to simulation of the *in silico* representations specified in claims 53 and 61, these dependent claims are not indefinite for failure to further define the base claims from which they depend. Applicant therefore respectfully requests withdrawal of this ground of rejection.

#### **Rejections Under 35 U.S.C. § 102**

Claims 49-51, 53-59 and 61-65 stand rejected under 35 U.S.C. § 102(b) as anticipated by Schilling et al. The Office alleges that Applicant is entitled to the filing date corresponding to the continuation application allegedly because the newly introduced claims constitute new matter. Schilling et al. is further alleged to anticipate the claimed invention because it was published prior to the filing date of the continuation application.

While not conceding that Schilling et al. describes each and every element of the invention claimed in claims 49-65, Applicant has set forth previously that the claims as filed in the continuation application are adequately supported in the application as of the priority date. Therefore, Schilling et al. does not constitute prior art and withdrawal of this ground of rejection is respectfully requested.

#### **Rejections Under 35 U.S.C. § 103**

Claims 52 and 60 stand rejected under 35 U.S.C. § 103(a) as obvious over Schilling et al. as applied to claims 49-51, 53-59 and 61-65 above and further because the use of BLAST would have been obvious to those skilled in the art allegedly because it is a well known search tool.

While not conceding that Schilling et al. teaches or suggests the claimed invention, Applicant has set forth previously that the claims as filed in the continuation application are adequately supported in the application. Therefore, Schilling et al. does not constitute prior art and withdrawal of this ground of rejection is respectfully requested.

Claims 49-65 stand rejected under 35 U.S.C. § 103(a) as being obvious over Blattner et al., Pennisi, Edwards et al. (1997) and Pramanik et al. The Office alleges that Blattner et al. describes the complete genomic sequence of *E. coli* and that Pennisi describes several sequenced microbial genomes and the functional assignment of open reading frames based on sequence homology. Edwards et al. is alleged to describe flux balance analysis of a metabolic network for *H. influenzae* based on homology of putative proteins using stoichiometric information and Pramanik et al. is alleged to describe a stoichiometric model of *E. coli* metabolism using flux balance analysis. The Office alleges that it would have been obvious to produce a stoichiometric matrix and an *in silico* model of *E. coli* and *H. influenzae* according to Pramanik et al. using the descriptions in Blattner et al. and Pennisi et al. because such models would have been of interest and within the skill of the art to produce as seen by Edwards et al. The Office further alleges that one skilled in the art would have been motivated to produce the invention as claimed in order to better understand and provide more robust models.

To establish *prima facie* obviousness of a claimed invention, the Office must show that the prior art would have suggested the claimed invention to one of ordinary skill in the art and that it could have been carried out with a reasonable likelihood of success when viewed in the light of the prior art. *Brown & Williamson Tobacco v. Philip Morris*, 229 F.3d 1120, 1124 (Fed. Cir. 2000). The first prong of this test is unsatisfied because the Office simply asserts that one skilled in the art would have been motivated to produce the claimed invention in order to better understand metabolism and to provide more robust models. However, there has been no showing that such a general conclusion is supported by the cited art.

Applicant respectfully submits that the Office has not established a *prima facie* case of obviousness at least because the cited references fail to provide a basis motivating one skilled in the art to combine the references to arrive at Applicant's claimed invention. The claimed invention is directed to obtaining a DNA sequence of a genome, determining open reading

frames of genes, assigning a function to proteins encoded by the open reading frames based on sequence homology, determining which genes are involved in cellular metabolism, determining substrates, products and stoichiometry for each metabolic gene and producing a genome specific stoichiometric matrix.

Applicant respectfully submits that there is no suggestion or motivation to combine at least Pramanik et al. with Edwards et al. to produce the claimed stoichiometric matrix or *in silico* representation. The additional references to Blattner et al. and Pennisi also fail to cure the deficiencies of Pramanik et al. and Edwards et al. because these references purport to describe genomic sequence information. In regard to Pramanik et al. and Edwards et al., Pramanik et al. is cited allegedly for describing the production of a stoichiometric model of *E. coli* metabolism using flux balance analysis. Edwards et al. is cited allegedly because it describes flux balance analysis of a metabolic network based on homology of putative proteins using stoichiometric information. However, and as described in the subject application at, for example, page 3, first paragraph, Pramanik et al. teach away from using models that are not produced from existing biochemical information. In contrast, Edwards et al. appear to describe a comparative flux balance analysis based on “hypothesized” metabolic pathways which do not use biochemical information. The cited combination of references fail to teach, suggest or provide a motivation to construct a stoichiometric matrix as claimed because Pramanik et al. teach away from generating a metabolic model absent actual knowledge of biochemical information. Therefore, Pramanik et al. is inapplicable in combination with a model purporting to use only genomic information such as Edwards et al. is alleged to describe. Accordingly, the cited art does not render the invention obvious and withdrawal of this ground of rejection is respectfully requested.

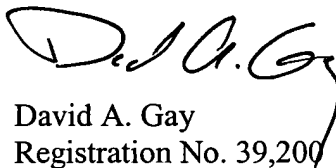
**CONCLUSION**

In light of the Amendments and Remarks herein, Applicant submits that the claims are in condition for allowance and respectfully requests a notice to this effect. Should the Examiner have any questions, he is invited to call the undersigned attorney

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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